ClinicalEvidence

# Wrinkles

**Search date April 2008**

*Juan Manríquez, Daniela Majerson Grinberg, and Claudia Nicklas Diaz.*

## ABSTRACT

INTRODUCTION: Skin disorders associated with photodamage from ultraviolet light include wrinkles, hyperpigmentation, tactile roughness, and telangiectasia, and are more common in people with white compared with other skin types. Wrinkles are also associated with ageing, hormonal status, smoking, and intercurrent disease. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of interventions to prevent and treat skin wrinkles? We searched: Medline, Embase, The Cochrane Library, and other important databases up to April 2008 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 20 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: alpha and beta hydroxyl acids, carbon dioxide laser, chemical peel, dermabrasion, facelifts, isotretinoin, natural cartilage polysaccharides (oral or topical), retinyl esters, sunscreens, tazarotene, tretinoin, variable pulse erbium:YAG laser, and vitamin C or E (topical).

## QUESTIONS



## INTERVENTIONS



## Key points

- Skin disorders associated with damage by ultraviolet light include wrinkles, hyperpigmentation, tactile roughness, and telangiectasia, and are more common in white people compared with other skin types.

  Wrinkles are also associated with ageing, hormonal status, smoking, and intercurrent disease.
- We don't know whether sunscreens or topical vitamins C or E prevent wrinkles, as no studies were found.
- Exposure to ultraviolet light may be associated with photodamage to the skin. Guidelines suggest that avoiding direct sunlight, either by staying indoors or in the shade, or by wearing protective clothing, is the most effective measure for reducing exposure to ultraviolet light.
- We don't know whether topical vitamins C or E improve the appearance of wrinkles, as studies have been small. These vitamins may cause stinging and erythema.
- Topical tretinoin improves fine wrinkles compared with placebo cream in people with mild to moderate photodamage, but its effect on coarse wrinkles is unclear.

  Topical tretinoin may cause itching, burning, erythema, and skin peeling.

  Isotretinoin cream improves fine and coarse wrinkles compared with vehicle cream in people with mild to severe photodamage, but causes severe irritation of the face in 5%–10% of people.

  We don't know whether tazarotene is more effective than tretinoin at improving fine and coarse wrinkles in people with moderate photodamage, as studies have given inconclusive results. It can cause burning of the skin.
- We don't know whether retinyl esters, topical or oral natural cartilage polysaccharides, alpha or beta hydroxyl acids, or chemical peels are beneficial.

- We don't know whether dermabrasion is more effective at improving wrinkles compared with carbon dioxide laser treatment, as studies have given inconclusive results, but adverse effects are common with both treatments, especially erythema.

  We don't know whether variable pulse erbium:YAG laser treatment or facelifts improve wrinkles, as few studies were found.

**DEFINITION**

Wrinkles are visible creases or folds in the skin. Wrinkles less than 1 mm in width and depth are defined as fine wrinkles and those greater than 1 mm as coarse wrinkles. Most RCTs have studied wrinkles on the face, forearms, and hands.

**INCIDENCE/ PREVALENCE**

We found no information on the incidence of wrinkles alone; only on the incidence of skin photodamage — which includes a spectrum of features such as wrinkles, hyperpigmentation, tactile roughness, and telangiectasia. The incidence of skin disorders associated with ultraviolet light increases with age and develops over several decades. One Australian study (1539 people, aged 20–55 years, living in Queensland) found moderate to severe photodamage in 72% of men and 47% of women under 30 years of age. [1] Severity of photodamage was significantly greater with increasing age, and was independently associated with solar keratoses and skin cancer. Wrinkling was more common in people with white skin (especially skin phototypes I and II). We found few reports of photodamage in black skin (phototypes V and VI). One study reported that the incidence of photodamage in European and North American populations with Fitzpatrick skin types I, II, and III is about 80%–90%. [2] As Asian skin is more pigmented (Fitzpatrick skin types III–V), wrinkling is not readily apparent until approximately the age of 50 years, with wrinkles being less severe than in white skin of similar age. A prospective study (85 white women living in North America and 70 Japanese women living in Tokyo, aged 20–69 years) comparing age-related changes in wrinkles in eight areas of the facial skin (forehead, glabella, upper eyelid, corner of the eye, lower eyelid, nasolabial groove, cheek, and corner of the mouth) and sagging in the subzygomatic area found more wrinkle formation in all areas of the face in younger age groups of white women than in Japanese women (aged 20–29 years). [3] Another prospective study (160 Chinese women and 160 French women, aged 20–60 years) found that wrinkle onset was delayed by about 10 years in Chinese women compared with French women. [4]

**AETIOLOGY/ RISK FACTORS**

Wrinkles may be caused by intrinsic factors (e.g., ageing, hormonal status, and intercurrent diseases) and by extrinsic factors (e.g., exposure to ultraviolet radiation, and cigarette smoke). These factors contribute to epidermal thinning, loss of elasticity, skin fragility, and creases and lines in the skin. The severity of photodamage varies with skin type, which includes skin colour, and the capacity to tan. [5] It is becoming increasingly clear that brief incidental sun exposures that occur during the activities of daily living add significantly to the average individual's daily exposure to ultraviolet light. One review of five observational studies found that facial wrinkles in men and women were more common in smokers than in non-smokers. [6] It also found that the risk of moderate to severe wrinkles in lifelong smokers was more than twice that in current smokers who had been smoking for a shorter period (RR 2.57, 95% CI 1.83 to 3.06). The effects of pregnancy and menopause on facial wrinkling have also been investigated by some researchers. In postmenopausal women, oestrogen deficiency is thought to be an important contributory factor for development of wrinkles. [7] One observational study (186 Korean women, aged 20–89 years) found that facial wrinkling increased significantly with an increase in the number of full-term pregnancies (OR 1.84, 95% CI 1.02 to 3.31) and the number of years since menopause (OR 3.91, 95% CI 1.07 to 14.28). [8] However, postmenopausal women who had HRT had significantly less facial wrinkling compared with postmenopausal women who had no history of HRT (OR 0.22, 95% CI 0.05 to 0.95). [8]

**PROGNOSIS**

Wrinkles cannot be considered a medical illness requiring intervention but concerns about changes in physical appearance brought on by aging can have a detrimental effect on quality of life. In some cases, concerns about physical appearance can affect personal interactions, occupational functioning, and self-esteem. [9] Geographical differences, culture, and personal values potentially influence a person's anxieties about ageing. In societies in which the maintenance of a youthful appearance is valued, the demand for interventions that ameliorate visible signs of ageing grows as ageing populations expand.

**AIMS OF INTERVENTION**

To prevent skin wrinkling; to improve fine and coarse wrinkling in adults; and to improve quality of life, with minimal adverse effects of treatment.

**OUTCOMES**

**Wrinkle improvement** includes physician and patient evaluation of improvement in skin texture that reduces the visibility of wrinkles; **quality of life**; and **adverse effects** of treatment. We excluded RCTs based solely on non-clinical outcomes, such as histological assessment, photography, or optical profilometry.

**METHODS**

*Clinical Evidence* search and appraisal April 2008. The following databases were used to identify studies for this systematic review: Medline 1966 to April 2008, Embase 1980 to April 2008, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2008, Issue 1. Additional searches were carried out using NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the author for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in any language, at least single-blinded, and containing more than 20 people of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. Most RCTs in the review recruited people with moderate to severe photodamage and wrinkles, rather than people with wrinkles alone. To aid readability of the numerical data in our reviews, we round percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as RRs and ORs. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 41 ). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

## QUESTION What are the effects of interventions to prevent skin wrinkles?

## OPTION SUNSCREENS

- For GRADE evaluation of interventions for Wrinkles, see table, p 41 .
- We don't know whether sunscreens prevent wrinkles, as no studies were found.
- Exposure to ultraviolet light may be associated with photodamage to the skin. Guidelines suggest that avoiding direct sunlight, either by staying indoors or in the shade, or by wearing protective clothing, is the most effective measure for reducing exposure to ultraviolet light.

### Benefits and harms

**Sunscreens:**

We found no systematic review or RCTs.

**Comment:**

We found two non-systematic reviews that reported the effects of sunscreens on the incidence of photodamage and skin cancer, but they did not assess the effectiveness of sunscreens in preventing wrinkles. [10] [11]

**Clinical guide:**

A history of mainly outdoor activities has been loosely linked with photodamage to the skin in men, but not in women. [12] Wrinkles caused by exposure to ultraviolet light — extrinsic ageing — may be prevented or partially reversed by avoiding direct sunlight; but this is not the case for wrinkles caused by intrinsic ageing. Guidelines developed by US Preventive Services Task Force suggest that staying indoors or in the shade, or wearing protective clothing, are the most effective measures for reducing exposure to ultraviolet light. However, no studies of sun avoidance to prevent photoageing, wrinkles, and skin cancer have been identified. [13]

## OPTION VITAMIN C OR E (TOPICAL)

- For GRADE evaluation of interventions for Wrinkles, see table, p 41 .

- We don't know whether topical vitamins C or E prevent wrinkles, as no studies were found.

## Benefits and harms

### Vitamin C or E (topical):

We found no systematic review or RCTs.

**Comment:** None.

## QUESTION What are the effects of treatments for skin wrinkles?

## OPTION TAZAROTENE

- For GRADE evaluation of interventions for Wrinkles, see table, p 41 .
- We don't know how tazarotene and tretinoin compare at improving fine and coarse wrinkles in people with moderate photodamage, as studies have given inconclusive results. It can cause burning of the skin.

## Benefits and harms

### Tazarotene versus vehicle cream:

We found one systematic review (search date 2002, [14] 2 RCTs) and one additional RCT. [15] One RCT identified by the review [14] reported on improvement of other outcomes in the forearm but not improvement in facial wrinkles, and therefore the data were not analysed.

**Wrinkle improvement**

*Tazarotene compared with placebo* Tazarotene may improve the appearance of wrinkles at 24 weeks (low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Improvement in fine wrinkles** | | | | | |
| [16] RCT **5-armed trial** | 349 people with moderate facial photodamage In review [14] The remaining arms evaluated tazarotene 0.025%, tazarotene 0.05%, and tazarotene 0.1% once-daily application for 24 weeks | **Physician-assessed improvement of fine facial wrinkling (6-point scale: 0 = none to 5 = very severe) , 24 weeks** 27/59 (46%) with tazarotene 0.01% (once-daily application for 24 weeks) 11/58 (19%) with vehicle cream (once-daily application for 24 weeks) | RR 2.41 95% CI 1.32 to 4.40 | ●● ○ | tazarotene 0.01% |
| [16] RCT **5-armed trial** | 349 people with moderate facial photodamage In review [14] The remaining arms evaluated tazarotene 0.01%, tazarotene 0.05%, and tazarotene 0.1% once-daily application for 24 weeks | **Physician-assessed improvement of fine facial wrinkling (6-point scale: 0 = none to 5 = very severe) , 24 weeks** 20/58 (34%) with tazarotene 0.025% (once-daily application for 24 weeks) 11/58 (19%) with vehicle cream (once-daily application for 24 weeks) | RR 1.82 95% CI 0.96 to 3.45 | ⟷ | Not significant |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| [16]<br>RCT<br>**5-armed trial** | 349 people with moderate facial photodamage<br>In review [14]<br>The remaining arms evaluated tazarotene 0.01%, tazarotene 0.025%, and tazarotene 0.1% once-daily application for 24 weeks | **Physician-assessed improvement of fine facial wrinkling (6-point scale: 0 = none to 5 = very severe) , 24 weeks**<br>28/58 (48%) with tazarotene 0.05% (once-daily application for 24 weeks)<br>11/58 (19%) with vehicle cream (once-daily application for 24 weeks) | RR 2.55<br>95% CI 1.40 to 4.61 | ●●○ | tazarotene 0.05% |
| [16]<br>RCT<br>**5-armed trial** | 349 people with moderate facial photodamage<br>In review [14]<br>The remaining arms evaluated tazarotene 0.01%, tazarotene 0.025%, and tazarotene 0.05% once-daily application for 24 weeks | **Physician-assessed improvement of fine facial wrinkling (6-point scale: 0 = none to 5 = very severe) , 24 weeks**<br>32/58 (55%) with tazarotene 0.1% (once-daily application for 24 weeks)<br>11/58 (19%) with vehicle cream (once-daily application for 24 weeks) | RR 2.91<br>95% CI 1.63 to 5.20 | ●●○ | tazarotene 0.1% |
| [15]<br>RCT | 563 adults with Fitzpatrick skin types I–IV, double blind | **Proportion of people with improved fine wrinkling by at least 1 grade on a 5-point scale , 24 weeks**<br>about 42% with tazarotene 0.1% (applied once daily for 24 weeks)<br>about 18% with placebo cream (applied once daily for 24 weeks)<br>Absolute results reported graphically | P <0.001 | ○○○ | tazarotene 0.1% |
| **Improvement in coarse wrinkles** | | | | | |
| [15]<br>RCT | 563 adults with Fitzpatrick skin types I–IV, double blind | **Proportion of people with improved coarse wrinkling by at least 1 grade on a 5-point scale , 24 weeks**<br>about 15% with tazarotene 0.1% (applied once daily for 24 weeks)<br>about 8% with placebo cream (applied once daily for 24 weeks)<br>Absolute results reported graphically | P <0.001 | ○○○ | tazarotene 0.1% |

## Quality of life

No data from the following reference on this outcome. [14] [15] [16]

## Adverse effects

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Adverse effects** | | | | | |
| [16]<br>RCT<br>**5-armed trial** | 349 people with moderate facial photodamage<br>In review [14] | **Adverse effects**<br>with tazarotene 0.01% (once-daily application for 24 weeks)<br>with tazarotene 0.025% (once-daily application for 24 weeks)<br>with tazarotene 0.05% (once-daily application for 24 weeks)<br>with tazarotene 0.1% (once-daily application for 24 weeks)<br>with vehicle cream (once-daily application for 24 weeks)<br>Most people reported adverse effects (249/349 [71%]). Most adverse effects were considered treatment related. The most frequent were signs and symptoms of local skin irritation, such as mild to moderate desquamation, burning sensation, erythema, pruritus, and dry skin | | | |
| [15]<br>RCT | 563 adults with Fitzpatrick skin types I–IV, double blind | **Desquamation**<br>105/283 (37%) with tazarotene 0.1% (applied once daily for 24 weeks)<br>8/280 (3%) with placebo cream (applied once daily for 24 weeks)<br>Adverse effects occurred mainly during the first 2 weeks of treatment, with the most common being desquamation, erythema, and burning | P <0.001 | ○○○ | placebo |
| [15]<br>RCT | 563 adults with Fitzpatrick skin types I–IV, double blind | **Erythema**<br>84/283 (30%) with tazarotene 0.1% (applied once daily for 24 weeks)<br>6/280 (2%) with placebo cream (applied once daily for 24 weeks)<br>Adverse effects occurred mainly during the first 2 weeks of treatment, with the most common being desquamation, erythema, and burning | P <0.001 | ○○○ | placebo |
| [15]<br>RCT | 563 adults with Fitzpatrick skin types I–IV, double blind | **Burning**<br>82/283 (29%) with tazarotene 0.1% (applied once daily for 24 weeks)<br>1/280 (0.4%) with placebo cream (applied once daily for 24 weeks)<br>Adverse effects occurred mainly during the first 2 weeks of treatment, with the most common being desquamation, erythema, and burning | P <0.001 | ○○○ | placebo |

### Tazarotene versus tretinoin:

We found one systematic review (search date 2002, [14] 1 RCT) and one additional RCT, [17] which both compared various concentrations of tazarotene versus 0.05% tretinoin.

### Wrinkle improvement

*Tazarotene compared with tretinoin* We don't know how tazarotene and tretinoin compare at improving wrinkles (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Improvement in fine wrinkles** | | | | | |
| [14] Systematic review | 117 people with moderate skin photodamage<br>Data from 1 RCT<br>5-armed trial<br>The remaining arms evaluated tazarotene 0.025%, tazarotene 0.05% and tazarotene 0.1% once-daily application for 24 weeks | **Proportion of people with improved fine facial wrinkles (physician-assessed using a 6-point scale: 0 = none to 5 = very severe) , 24 weeks**<br>27/59 (46%) with tazarotene 0.01% (applied once daily for 24 weeks)<br>32/58 (55%) with tretinoin 0.05% (applied once daily for 24 weeks) | RR 1.21<br>95% CI 0.84 to 1.73 | ⟷ | Not significant |
| [14] Systematic review | 117 people with moderate skin photodamage<br>Data from 1 RCT<br>5-armed trial<br>The remaining arms evaluated tazarotene 0.01%, tazarotene 0.05% and tazarotene 0.1% once-daily application for 24 weeks | **Proportion of people with improved fine facial wrinkles (physician-assessed using a 6-point scale: 0 = none to 5 = very severe) , 24 weeks**<br>20/58 (34%) with tazarotene 0.025% (applied once daily for 24 weeks)<br>32/58 (55%) with tretinoin 0.05% (applied once daily for 24 weeks) | RR 1.60<br>95% CI 1.05 to 2.44 | ●○○ | tretinoin 0.05% |
| [14] Systematic review | 117 people with moderate skin photodamage<br>Data from 1 RCT<br>5-armed trial<br>The remaining arms evaluated tazarotene 0.01%, tazarotene 0.025% and tazarotene 0.1% once-daily application for 24 weeks | **Proportion of people with improved fine facial wrinkles (physician-assessed using a 6-point scale: 0 = none to 5 = very severe) , 24 weeks**<br>28/58 (48%) with tazarotene 0.05% (applied once daily for 24 weeks)<br>32/58 (55%) with tretinoin 0.05% (applied once daily for 24 weeks) | RR 1.14<br>95% CI 0.80 to 1.63 | ⟷ | Not significant |
| [14] Systematic review | 117 people with moderate skin photodamage<br>Data from 1 RCT<br>5-armed trial<br>The remaining arms evaluated tazarotene 0.01%, tazarotene 0.025% and tazarotene 0.05% once-daily application for 24 weeks | **Proportion of people with improved fine facial wrinkles (physician-assessed using a 6-point scale: 0 = none to 5 = very severe) , 24 weeks**<br>32/58 (55%) with tazarotene 0.1% (applied once daily for 24 weeks)<br>32/58 (55%) with tretinoin 0.05% (applied once daily for 24 weeks) | RR 1.00<br>95% CI 0.72 to 1.39 | ⟷ | Not significant |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| [17]<br>RCT | 173 people, mean age 55 years, with Fitzpatrick skin types I–IV | **Proportion of people with improved fine wrinkling by at least 1 grade on a 5-point scale , 24 weeks**<br>70/88 (80%) with tazarotene 0.1% (applied once daily in the evening for 24 weeks)<br>53/85 (62%) with tretinoin 0.05% (applied once daily in the evening for 24 weeks) | P <0.01 | ○○○ | tazarotene 0.1% |
| **Improvement in coarse wrinkles** | | | | | |
| [17]<br>RCT | 173 people, mean age 55 years, with Fitzpatrick skin types I–IV | **Proportion of people with improved coarse wrinkling by at least 1 grade on a 5-point scale , 24 weeks**<br>34/88 (39%) with tazarotene 0.1% (applied once daily in the evening for 24 weeks)<br>29/85 (32%) with tretinoin 0.05% (applied once daily in the evening for 24 weeks) | P <0.05 | ○○○ | tazarotene 0.1% |

## Quality of life

No data from the following reference on this outcome. [14] [17]

## Adverse effects

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Adverse effects** | | | | | |
| [14]<br>Systematic review | 117 people with moderate skin photodamage<br>Data from 1 RCT<br>5-armed tria<br>The remaining arms evaluated tazarotene 0.025%, tazarotene 0.05%, and tazarotene 0.1% once-daily application for 24 weeks | **Adverse effects (overall)**<br>2/58 (3%) with tazarotene 0.01% (applied once daily for 24 weeks)<br>3/58 (5%) with tretinoin 0.05% (applied once daily for 24 weeks)<br>Skin irritation, burning, peeling, dryness, erythema, and itching were the most common adverse effects with both tazarotene and tretinoin | RR 1.50<br>95% CI 0.26 to 8.65 | ⟷ | Not significant |
| [14]<br>Systematic review | 117 people with moderate skin photodamage<br>Data from 1 RCT<br>5-armed trial<br>The remaining arms evaluated tazarotene 0.025%, | **Adverse effects**<br>0/58 (0%) with tazarotene 0.025% (applied once daily for 24 weeks)<br>3/58 (5%) with tretinoin 0.05% (applied once daily for 24 weeks)<br>Skin irritation, burning, peeling, dryness, erythema, and itching were the most common adverse | RR 7.0<br>95% CI 0.37 to 132.56 | ⟷ | Not significant |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| | tazarotene 0.05%, and tazarotene 0.1% once-daily application for 24 weeks | effects with both tazarotene and tretinoin | | | |
| [14]<br>Systematic review | 117 people with moderate skin photodamage<br>Data from 1 RCT<br>5-armed trial<br>The remaining arms evaluated tazarotene 0.025%, tazarotene 0.05%, and tazarotene 0.1% once-daily application for 24 weeks | **Adverse effects**<br>2/58 (3%) with tazarotene 0.05% (applied once daily for 24 weeks)<br>3/58 (5%) with tretinoin 0.05% (applied once daily for 24 weeks)<br>Skin irritation, burning, peeling, dryness, erythema, and itching were the most common adverse effects with both tazarotene and tretinoin | RR 1.50<br>95% CI 0.26 to 8.65 | ⟷ | Not significant |
| [14]<br>Systematic review | 117 people with moderate skin photodamage<br>Data from 1 RCT<br>5-armed trial; the remaining arms evaluated tazarotene 0.025%, tazarotene 0.05%, and tazarotene 0.1% once-daily application for 24 weeks | **Adverse effects**<br>2/58 (3%) with tazarotene 0.1% (applied once daily for 24 weeks)<br>3/58 (5%) with tretinoin 0.05% (applied once daily for 24 weeks)<br>Skin irritation, burning, peeling, dryness, erythema, and itching were the most common adverse effects with both tazarotene and tretinoin | RR 1.50<br>95% CI 0.26 to 8.65 | ⟷ | Not significant |
| [17]<br>RCT | 173 people, mean age 55 years, with Fitzpatrick skin types I–IV | **Sensation of burning on the skin**<br>15% with tazarotene 0.1% (applied once daily in the evening for 24 weeks)<br>0% with tretinoin 0.05% (applied once daily in the evening for 24 weeks)<br>Absolute numbers not reported<br>Adverse effects were all of mild to moderate severity, and occurred most frequently in the first week of treatment | Reported as significant<br>P value not reported | ○○○ | tretinoin |
| [17]<br>RCT | 173 people, mean age 55 years, with Fitzpatrick skin types I–IV | **Irritation**<br>21% with tazarotene 0.1% (applied once daily in the evening for 24 weeks)<br>35% with tretinoin 0.05% (applied once daily in the evening for 24 weeks)<br>Absolute numbers not reported<br>Adverse effects were all of mild to moderate severity, and occurred most frequently in the first week of treatment | Reported as not significant<br>P value not reported | ⟷ | Not significant |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| [17]<br>RCT | 173 people, mean age 55 years, with Fitzpatrick skin types I–IV | **Dryness**<br>9% with tazarotene 0.1% (applied once daily in the evening for 24 weeks)<br>15% with tretinoin 0.05% (applied once daily in the evening for 24 weeks)<br>Absolute numbers not reported<br>Adverse effects were all of mild to moderate severity, and occurred most frequently in the first week of treatment | Reported as not significant<br>P value not reported | ⟷ | Not significant |
| [17]<br>RCT | 173 people, mean age 55 years, with Fitzpatrick skin types I–IV | **Peeling**<br>12% with tazarotene 0.1% (applied once daily in the evening for 24 weeks)<br>11% with tretinoin 0.05% (applied once daily in the evening for 24 weeks)<br>Absolute numbers not reported<br>Adverse effects were all of mild to moderate severity, and occurred most frequently in the first week of treatment | Reported as not significant<br>P value not reported | ⟷ | Not significant |
| [17]<br>RCT | 173 people, mean age 55 years, with Fitzpatrick skin types I–IV | **Redness**<br>10% with tazarotene 0.1% (applied once daily in the evening for 24 weeks)<br>7% with tretinoin 0.05% (applied once daily in the evening for 24 weeks)<br>Absolute numbers not reported<br>Adverse effects were all of mild to moderate severity, and occurred most frequently in the first week of treatment | Reported as not significant<br>P value not reported | ⟷ | Not significant |
| [17]<br>RCT | 173 people, mean age 55 years, with Fitzpatrick skin types I–IV | **Erythema**<br>3% with tazarotene 0.1% (applied once daily in the evening for 24 weeks)<br>4% with tretinoin 0.05% (applied once daily in the evening for 24 weeks)<br>Absolute numbers not reported<br>Adverse effects were all of mild to moderate severity, and occurred most frequently in the first week of treatment | Reported as not significant<br>P value not reported | ⟷ | Not significant |
| [17]<br>RCT | 173 people, mean age 55 years, with Fitzpatrick skin types I–IV | **Stinging**<br>3% with tazarotene 0.1% (applied once daily in the evening for 24 weeks)<br>6% with tretinoin 0.05% (applied once daily in the evening for 24 weeks)<br>Absolute numbers not reported<br>Adverse effects were all of mild to moderate severity, and oc- | Reported as not significant<br>P value not reported | ⟷ | Not significant |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| | | curred most frequently in the first week of treatment | | | |
| [17]<br>RCT | 173 people, mean age 55 years, with Fitzpatrick skin types I–IV | **Itching**<br>3% with tazarotene 0.1% (applied once daily in the evening for 24 weeks)<br>4% with tretinoin 0.05% (applied once daily in the evening for 24 weeks)<br>Absolute numbers not reported<br>Adverse effects were all of mild to moderate severity, and oc-curred most frequently in the first week of treatment | Reported as not significant<br>P value not reported | ⟷ | Not significant |

**Further information on studies**

**Comment:** None.

## OPTION TRETINOIN

- For GRADE evaluation of interventions for Wrinkles, see table, p 41 .
- Topical tretinoin improves fine wrinkles compared with placebo cream in people with mild to moderate photodamage, but its effect on coarse wrinkles is unclear.
- Topical tretinoin may cause itching, burning, erythema, and skin peeling.

## Benefits and harms

### Tretinoin versus placebo:

We found one systematic review (search date 2002, 12 RCTs), which separately compared the effects of various concentrations of tretinoin (0.1%, 0.05%, 0.025%, 0.02%, 0.01%, and 0.001%) versus placebo. [14] We also found one subsequent RCT. [18]

#### Wrinkle improvement

*Tretinoin compared with placebo* Daily application of tretinoin at concentrations above 0.02% may be more effective than placebo at improving facial fine and coarse wrinkles at 16 to 48 weeks in people with mild to moderate and moderate to severe photodamage. However, daily application of tretinoin at concentrations lower than 0.02% (0.001%–0.01%) may be no more effective than placebo at improving wrinkles (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Improvement in fine wrinkles (tretinoin 0.001%)** | | | | | |
| [14]<br>Systematic review | 147 people with mild to moderate photodamage<br>Data from 1 RCT | **Proportion of people with improved fine facial wrinkles (physician-assessed) , 24 weeks**<br>20/75 (27%) with topical tretinoin 0.001% (once daily for 24 weeks)<br>28/72 (39%) with vehicle cream (once daily for 24 weeks) | RR 0.69<br>95% CI 0.43 to 1.10<br>RCTs identified by review had methodological limitations; see further information on studies for full details | ⟷ | Not significant |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Improvement in fine wrinkles (tretinoin 0.01%)** | | | | | |
| [14] Systematic review | 345 people with mild to moderate photodamage<br>3 RCTs in this analysis | **Proportion of people with improved fine facial wrinkles (physician-assessed) , 24 weeks**<br>93/174 (53%) with topical tretinoin 0.01% (once daily for 24 weeks)<br>63/171 (37%) with vehicle cream (once daily for 24 weeks) | RR 1.57<br>95% CI 0.91 to 2.71<br>RCTs identified by review had methodological limitations; see further information on studies for full details | ⟷ | Not significant |
| [14] Systematic review | 34 people with mild to moderate photodamage of the face and forearms<br>Data from 1 RCT<br>Within participant comparison (opposite arms) | **Proportion of people with improved fine forearm wrinkles (physician-assessed) , 24 weeks**<br>24/34 (71%) with topical tretinoin 0.01% (once daily for 24 weeks)<br>1/34 (3%) with vehicle cream (once daily for 24 weeks)<br>Patients were randomised to use tretinoin on either their right or left forearm, and placebo on the other arm | P <0.01<br>RCTs identified by review had methodological limitations; see further information on studies for full details | ○○○ | tretinoin 0.01% |
| **Improvement in fine wrinkles (tretinoin 0.02%)** | | | | | |
| [14] Systematic review | 328 people with moderate to severe photodamage<br>2 RCTs in this analysis | **Proportion of people with improved fine facial wrinkles (physician-assessed) , 24 weeks**<br>98/159 (62%) with topical tretinoin 0.02% (once daily for 24 weeks)<br>65/169 (39%) with vehicle cream (once daily for 24 weeks) | RR 1.60<br>95% CI 1.28 to 2.01<br>RCTs identified by review had methodological limitations; see further information on studies for full details | ●○○ | tretinoin 0.02% |
| **Improvement in fine wrinkles (tretinoin 0.025%)** | | | | | |
| [14] Systematic review | 67 people with moderate to severe photodamage<br>Data from 1 RCT | **Mean improvement in fine facial wrinkle score (physician-assessed using a 10-point scale) , 48 weeks**<br>1.3 with topical tretinoin 0.025% (once daily for 48 weeks)<br>0.6 with vehicle cream (once daily for 48 weeks) | WMD 0.75<br>95% CI 0.22 to 1.28<br>RCTs identified by review had methodological limitations; see further information on studies for full details | ○○○ | tretinoin 0.025% |
| **Improvement in fine wrinkles (tretinoin 0.05%)** | | | | | |
| [14] Systematic review | 593 people with mild to moderate photodamage<br>5 RCTs in this analysis | **Proportion of people with improved fine facial wrinkles , 24 weeks**<br>186/298 (62%) with topical tretinoin 0.05% (once daily for 24 weeks)<br>102/295 (35%) with vehicle cream (once daily for 24 weeks) | RR 1.76<br>95% CI 1.47 to 2.12<br>RCTs identified by review had methodological limitations; see further information on studies for full details | ●○○ | tretinoin 0.05% |
| [14] Systematic review | 125 people with mild to moderate photodamage<br>Data from 1 RCT | **Proportion of people with improved fine forearm wrinkles (physician-assessed) , 24 weeks**<br>32/62 (52%) with topical tretinoin 0.05% (once daily for 24 weeks)<br>22/63 (35%) with vehicle cream (once daily for 24 weeks) | RR 1.48<br>95% CI 0.98 to 2.24<br>RCTs identified by review had methodological limitations; see further information on studies for full details | ⟷ | Not significant |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Improvement in fine wrinkles (tretinoin 0.1%)** | | | | | |
| [14]<br>Systematic review | 30 people with photodamage of the face and forearms<br>Data from 1 RCT | **Proportion of people with improved fine facial wrinkles (physician-assessed) , 16 weeks**<br>14/15 (93%) with topical tretinoin 0.1% (once daily for 16 weeks)<br>0/15 (0%) with vehicle cream (once daily for 16 weeks) | RR 29.00<br>95% CI 1.89 to 445.86<br>RCTs identified by review had methodological limitations; see further information on studies for full details | ●●● | tretinoin 0.1% |
| [14]<br>Systematic review | 30 people<br>Data from 1 RCT<br>Within participant comparison (opposite arms) | **Proportion of people with improved fine forearm wrinkles , 16 weeks**<br>30/30 (100%) with topical tretinoin 0.1% (once daily for 16 weeks)<br>0/30 (0%) with vehicle cream (once daily for 16 weeks)<br>Patients were randomised to use tretinoin on either their right or left forearm, and placebo on the other arm | P <0.001<br>RCTs identified by review had methodological limitations; see further information on studies for full details | ○○○ | tretinoin 0.1% |
| [18]<br>RCT | 45 people with moderate to severe facial photodamage | **Proportion of people with improved fine facial wrinkles (physician- and patient-assessed) , 6 months**<br>94% with tretinoin 0.1% (microsphere gel preparation; applied once daily for 6 months)<br>23% with vehicle gel (applied once daily for 6 months)<br>Absolute numbers not reported | P <0.0001<br>Method of randomisation and allocation concealment were unclear | ○○○ | tretinoin 0.1% |
| **Improvement in coarse wrinkles (tretinoin 0.01%)** | | | | | |
| [14]<br>Systematic review | 34 people with mild to moderate photodamage of the face and forearms<br>Data from 1 RCT | **Proportion of people with improved coarse facial wrinkles (physician-assessed) , 24 weeks**<br>7/17 (41%) with topical tretinoin 0.01% (once daily for 24 weeks)<br>1/17 (6%) with vehicle cream (once daily for 24 weeks) | RR 7.00<br>95% CI 0.96 to 50.93<br>RCTs identified by review had methodological limitations; see further information on studies for full details | ⟷ | Not significant |
| **Improvement in coarse wrinkles (tretinoin 0.02%)** | | | | | |
| [14]<br>Systematic review | 328 people with moderate to severe photodamage<br>2 RCTs in this analysis | **Proportion of people with improved coarse facial wrinkles (physician-assessed) , 24 weeks**<br>64/159 (40%) with topical tretinoin 0.02% (once daily for 24 weeks)<br>40/169 (24%) with vehicle cream (once daily for 24 weeks) | RR 1.70<br>95% CI 1.22 to 2.37<br>RCTs identified by review had methodological limitations; see further information on studies for full details | ●○○ | tretinoin 0.02% |
| **Improvement in coarse wrinkles (tretinoin 0.05%)** | | | | | |
| [14]<br>Systematic review | 162 people with mild to moderate photodamage<br>2 RCTs in this analysis | **Proportion of people with improved coarse facial wrinkles (physician-assessed) , 24 weeks**<br>41/79 (52%) with topical tretinoin 0.05% (once daily for 24 weeks) | RR 1.68<br>95% CI 1.17 to 2.42<br>RCTs identified by review had methodological limitations; see further information on studies for full details | ●○○ | tretinoin 0.05% |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| | | 25/83 (30%) with vehicle cream (once daily for 24 weeks) | | | |
| **Improvement in coarse wrinkles (tretinoin 0.1%)** | | | | | |
| [14]<br>Systematic review | 30 people with mild to moderate photodamage of the face and forearms<br>Data from 1 RCT | **Proportion of people with improved coarse facial wrinkles (physician-assessed) , 16 weeks**<br>6/15 (40%) with topical tretinoin 0.1% (once daily for 16 weeks)<br>0/15 (0%) with vehicle cream (once daily for 16 weeks) | RR 13.0<br>95% CI 0.80 to 212.02<br>RCTs identified by review had methodological limitations; see further information on studies for full details | ⟷ | Not significant |
| [14]<br>Systematic review | 30 people<br>Data from 1 RCT<br>Within participant comparison (opposite arms) | **Proportion of people with improved coarse forearm wrinkles , 16 weeks**<br>9/30 (30%) with topical tretinoin 0.1% (once daily for 16 weeks)<br>0/30 (0%) with vehicle cream (once daily for 16 weeks)<br>Patients were randomised to use tretinoin on either their right or left forearm, and placebo on the other arm | P <0.01<br>RCTs identified by review had methodological limitations; see further information on studies for full details | ○○○ | tretinoin 0.1% |
| [18]<br>RCT | 45 people with moderate to severe facial photodamage | **Proportion of people with improved coarse facial wrinkles (physician- and patient-assessed) , 6 months**<br>22% with tretinoin 0.1% (microsphere gel preparation; applied once daily for 6 months)<br>5% with vehicle gel (applied once daily for 6 months)<br>Absolute numbers not reported | P = 0.1<br>Method of randomisation and allocation concealment were unclear | ⟷ | Not significant |
| **Improvement in wrinkles (global; tretinoin 0.1%)** | | | | | |
| [18]<br>RCT | 45 people with moderate to severe facial photodamage | **Global assessment score (investigators and participants scored signs of photodamage and skin irritation, using a scale from 0–9 [0 = none, 1–3 = mild, 4–6 = moderate, 7–9 = severe]) , 6 months**<br>with tretinoin 0.1% (microsphere gel preparation; applied once daily for 6 months)<br>with vehicle gel (applied once daily for 6 months)<br>Absolute results reported graphically<br>The RCT reported a significant increase in the proportion of people improved with tretinoin compared with vehicle gel | P <0.0003<br>Method of randomisation and allocation concealment were unclear | ○○○ | tretinoin 0.1% |
| [18]<br>RCT | 45 people with moderate to severe facial photodamage | **Proportion of people with improved facial tactile roughness (physician- and patient-assessed) , 6 months**<br>83% with tretinoin 0.1% (microsphere gel preparation; applied once daily for 6 months) | P = 0.53<br>Method of randomisation and allocation concealment were unclear | ⟷ | Not significant |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| | | 91% with vehicle gel (applied once daily for 6 months)<br>Absolute numbers not reported | | | |

### Quality of life

No data from the following reference on this outcome. [14] [18]

### Adverse effects

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Adverse effects (tretinoin 0.01%)** | | | | | |
| [14]<br>Systematic review | 344 people with mild to moderate photodamage<br>2 RCTs in this analysis | **Burning or stinging , 24 weeks**<br>36/173 (21%) with topical tretinoin 0.01% (once daily for 24 weeks)<br>18/171 (11%) with vehicle cream (once daily for 24 weeks)<br>See further information on studies for details on most common adverse effects associated with tretinoin | RR 1.99<br>95% CI 1.20 to 3.32 | ●○○ | vehicle cream |
| **Adverse effects (tretinoin 0.05%)** | | | | | |
| [14]<br>Systematic review | 349 people<br>2 RCTs in this analysis | **Erythema , 24 weeks**<br>60/178 (34%) with topical tretinoin 0.05% (once daily for 24 weeks)<br>16/171 (9%) with vehicle cream (once daily for 24 weeks)<br>See further information on studies for details on most common adverse effects associated with tretinoin | RR 3.58<br>95% CI 1.99 to 6.46 | ●●○ | vehicle cream |
| [14]<br>Systematic review | 349 people<br>2 RCTs in this analysis | **Scaling/dryness , 24 weeks**<br>115/178 (65%) with topical tretinoin 0.05% (once daily for 24 weeks)<br>49/171 (29%) with vehicle cream (once daily for 24 weeks)<br>See further information on studies for details on most common adverse effects associated with tretinoin | RR 2.23<br>95% CI 1.72 to 2.88 | ●●○ | vehicle cream |
| [14]<br>Systematic review | 349 people<br>2 RCTs in this analysis | **Burning and stinging , 24 weeks**<br>69/178 (39%) with topical tretinoin 0.05% (once daily for 24 weeks)<br>18/171 (11%) with vehicle cream (once daily for 24 weeks) | RR 3.75<br>95% CI 2.35 to 5.98 | ●●○ | vehicle cream |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| | | See further information on studies for details on most common adverse effects associated with tretinoin | | | |
| **Adverse effects (tretinoin 0.1%)** | | | | | |
| [14] Systematic review | 76 people with moderate to severe photodamage of the face and forearms<br>Data from 1 RCT | **Erythema , 48 weeks**<br>16/36 (44%) with topical tretinoin 0.1% (once daily for 48 weeks)<br>0/40 (0%) with vehicle cream (once daily for 48 weeks)<br>See further information on studies for details on most common adverse effects associated with tretinoin | RR 36.57<br>95% CI 2.27 to 588.35 | ●●● | vehicle cream |
| [18] RCT | 45 people with moderate to severe facial photodamage | **Skin erythema , 1 month**<br>with tretinoin 0.1% (microsphere gel preparation; applied once daily for 6 months)<br>with vehicle gel (applied once daily for 6 months)<br>Absolute results not reported<br>RCT reported that tretinoin 0.1% increased the severity of skin erythema compared with vehicle gel | P = 0.0005<br>Method of randomisation and allocation concealment were unclear | ○○○ | vehicle gel |
| [18] RCT | 45 people with moderate to severe facial photodamage | **Peeling , 1 month**<br>with tretinoin 0.1% (microsphere gel preparation; applied once daily for 6 months)<br>with vehicle gel (applied once daily for 6 months)<br>Absolute results not reported<br>RCT reported that tretinoin 0.1% increased the severity of peeling compared with vehicle gel | P <0.0001<br>Method of randomisation and allocation concealment were unclear | ○○○ | vehicle gel |
| [18] RCT | 45 people with moderate to severe facial photodamage | **Dryness , 1 month**<br>with tretinoin 0.1% (microsphere gel preparation; applied once daily for 6 months)<br>with vehicle gel (applied once daily for 6 months)<br>Absolute results not reported<br>RCT reported that tretinoin 0.1% increased the severity of dryness compared with vehicle gel | P <0.0001<br>Method of randomisation and allocation concealment were unclear | ○○○ | vehicle gel |
| [18] RCT | 45 people with moderate to severe facial photodamage | **Itching , 1 month**<br>with tretinoin 0.1% (microsphere gel preparation; applied once daily for 6 months)<br>with vehicle gel (applied once daily for 6 months)<br>Absolute results not reported<br>RCT reported that tretinoin 0.1% increased the severity of itching compared with vehicle gel | P = 0.0005<br>Method of randomisation and allocation concealment were unclear | ○○○ | vehicle gel |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| [18] RCT | 45 people with moderate to severe facial photodamage | **Burning/stinging , 1 month** with tretinoin 0.1% (microsphere gel preparation; applied once daily for 6 months) with vehicle gel (applied once daily for 6 months) Absolute results not reported RCT reported that tretinoin 0.1% increased the severity of burning/stinging compared with vehicle gel | P <0.0001 Method of randomisation and allocation concealment were unclear | ○○○ | vehicle gel |
| [18] RCT | 45 people with moderate to severe facial photodamage | **Peeling , 6 months** with tretinoin 0.1% (microsphere gel preparation; applied once daily for 6 months) with vehicle gel (applied once daily for 6 months) Absolute results not reported RCT reported that tretinoin 0.1% increased the severity of peeling compared with vehicle gel | P = 0.001 Method of randomisation and allocation concealment were unclear | ○○○ | vehicle gel |
| [18] RCT | 45 people with moderate to severe facial photodamage | **Dryness , 6 months** with tretinoin 0.1% (microsphere gel preparation; applied once daily for 6 months) with vehicle gel (applied once daily for 6 months) Absolute results not reported RCT reported that tretinoin 0.1% increased the severity of dryness compared with vehicle gel | P = 0.007 Method of randomisation and allocation concealment were unclear | ○○○ | vehicle gel |

**Tretinoin versus tazarotene:**

See option on tazarotene, p 4 .

**Further information on studies**

[14] **Methodological limitations** The RCTs included in the systematic review are limited by their small sample sizes, short duration, and inconsistencies among investigator and participant assessments. The methods of randomisation and allocation concealment were unclear in most RCTs in the systematic review. **Adverse effects of tretinoin** The systematic review found that all strengths of tretinoin were associated with adverse effects. The most common adverse effects were itching, burning/stinging, dryness, and erythema, which peaked during the first 2 weeks and decreased with time.

**Comment:** We found individual case reports of congenital defects associated with topical tretinoin used during the first trimester of pregnancy. [19] [20] We found one observational study that identified 215 case histories of women who used tretinoin cream for acne during the first trimester of pregnancy, and compared them with 430 age-matched, non-exposed women who delivered infants at the same hospital. [21] The study found no significant difference in the incidence of major congenital disorders (1.9% with tretinoin *v* 2.6% with control; RR 0.7, 95% CI 0.2 to 2.3).

## OPTION ISOTRETINOIN

- For GRADE evaluation of interventions for Wrinkles, see table, p 41 .
- Isotretinoin cream improves fine and coarse wrinkles compared with vehicle cream in people with mild to severe photodamage, but causes severe irritation of the face in 5–10% of people.
- Isotretinoin is associated with increased facial erythema, scaling/dryness, and burning/stinging compared with placebo cream.

## Benefits and harms

### Isotretinoin versus placebo:

We found one systematic review (search date 2002), [14] which included one RCT comparing isotretinoin versus placebo. We also found one additional RCT. [22]

#### Wrinkle improvement

*Isotretinoin compared with placebo* Isotretinoin cream (0.1%) may be more effective than placebo at improving facial fine and coarse wrinkles and forearm wrinkles after 36 weeks in people with moderate to severe photodamage (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Improvement in fine wrinkles** | | | | | |
| [14] Systematic review | 681 people with moderate to severe facial photodamage, and mild to severe photodamage of arms and hands<br>Data from 1 RCT | **Improvement in fine facial wrinkles , 36 weeks**<br>with topical isotretinoin 0.1% (0.5 g) (applied once daily for 36 weeks)<br>with vehicle cream (applied once daily for 36 weeks) | WMD 4.90<br>95% CI 3.79 to 6.01 | ○○○ | isotretinoin 0.1% |
| [14] Systematic review | 681 people with moderate to severe facial photodamage, and mild to severe photodamage of arms and hands<br>Data from 1 RCT | **Improvement in fine wrinkles of the forearm , 36 weeks**<br>with topical isotretinoin 0.1% (0.5 g) (applied once daily for 36 weeks)<br>with vehicle cream (applied once daily for 36 weeks) | WMD 3.0<br>95% CI 2.17 to 3.83 | ○○○ | isotretinoin 0.1% |
| [22] RCT | 776 people in 17 US centres, aged 20–76 years, with mild to moderate facial photodamage | **Physician-assessed improvement of fine facial wrinkling (change from baseline measured on 100 mm VAS: –50 = worse, 0 = no change, +50 = better) , 36 weeks**<br>+7.4 with topical isotretinoin 0.05% (applied once daily for 12 weeks), followed by isotretinoin 0.01% (applied for the next 24 weeks)<br>+5.3 with vehicle cream (applied for 36 weeks)<br>Analysis of 613 people (79%) at 36 weeks; analysis was not by intention to treat<br>Change in fine wrinkles was also assessed by 5 dermatologists; see further information on studies for details of findings | P <0.01 | ○○○ | isotretinoin |
| [22] RCT | 776 people in 17 US centres, aged 20–76 years, with mild to moderate | **Participant-assessed improvement of fine facial wrinkling (change from baseline measured on 100 mm VAS: –50 =** | P <0.01 | ○○○ | isotretinoin |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| | facial photodamage | **worse, 0 = no change, +50 = better) , 36 weeks**<br>+11.7 with topical isotretinoin 0.05% (applied once daily for 12 weeks), followed by isotretinoin 0.01% (applied daily for the next 24 weeks)<br>+7.9 with vehicle cream (applied for 36 weeks)<br>Analysis of 613 people (79%) at 36 weeks; analysis was not by intention to treat<br>Change in fine wrinkles was also assessed by 5 dermatologists; see further information on studies for details of findings | | | |
| **Improvement in coarse wrinkles** | | | | | |
| [14]<br>Systematic review | 681 people with moderate to severe facial photodamage, and mild to severe photodamage of arms and hands<br>Data from 1 RCT | **Improvement in coarse facial wrinkles , 36 weeks**<br>with topical isotretinoin 0.1% (0.5 g) (applied once daily for 36 weeks)<br>with vehicle cream (applied once daily for 36 weeks) | WMD 3.0<br>95% CI 2.17 to 3.83 | ○○○ | isotretinoin 0.1% |
| **Improvement in wrinkles (global)** | | | | | |
| [22]<br>RCT | 776 people in 17 US centres, aged 20–76 years, with mild to moderate facial photodamage | **Physician-assessed overall skin appearance (change from baseline measured on 100 mm VAS: –50 = worse, 0 = no change, +50 = better) , 36 weeks**<br>+8.3 with topical isotretinoin 0.05% (applied once daily for 12 weeks), followed by isotretinoin 0.01% (applied for the next 24 weeks)<br>+6.4 with vehicle cream (applied for 36 weeks)<br>Analysis of 613 people (79%) at 36 weeks; analysis was not by intention to treat | P <0.01 | ○○○ | isotretinoin |
| [22]<br>RCT | 776 people in 17 US centres, aged 20–76 years, with mild to moderate facial photodamage | **Participant-assessed overall skin appearance (change from baseline measured on 100 mm VAS: –50 = worse, 0 = no change, +50 = better) , 36 weeks**<br>with topical isotretinoin 0.05% (applied once daily for 12 weeks), followed by isotretinoin 0.01% (applied for the next 24 weeks)<br>with vehicle cream (appled for 36 weeks)<br>Analysis of 613 people (79%) at 36 weeks; analysis was not by intention to treat | Reported as not significant<br>P value not reported | ⟷ | Not significant |

## Quality of life

No data from the following reference on this outcome. [14] [22]

### Adverse effects

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Adverse effects** | | | | | |
| [14] Systematic review | 681 people with moderate to severe facial photodamage, and mild to severe photodamage of arms and hands<br>Data from 1 RCT | **Withdrawal because of adverse effects**<br>25/323 (8%) with topical isotretinoin 0.1% (0.5 g) (applied once daily for 36 weeks)<br>9/353 (3%) with vehicle cream (applied once daily for 36 weeks) | Significance not assessed | | |
| [14] Systematic review | 681 people with moderate to severe facial photodamage, and mild to severe photodamage of arms and hands<br>Data from 1 RCT | **Erythema**<br>210/323 (65%) with topical isotretinoin 0.1% (0.5 g; applied once daily for 36 weeks)<br>90/358 (25%) with vehicle cream (applied once daily for 36 weeks) | RR 2.59<br>95% CI 2.13 to 3.15 | ●●○ | vehicle cream |
| [14] Systematic review | 681 people with moderate to severe facial photodamage, and mild to severe photodamage of arms and hands<br>Data from 1 RCT | **Scaling/dryness**<br>175/323 (54%) with topical isotretinoin 0.1% (0.5 g; applied once daily for 36 weeks)<br>30/358 (8%) with vehicle cream (applied once daily for 36 weeks) | RR 6.47<br>95% CI 4.52 to 9.24 | ●●● | vehicle cream |
| [14] Systematic review | 681 people with moderate to severe facial photodamage, and mild to severe photodamage of arms and hands<br>Data from 1 RCT | **Burning/stinging**<br>214/323 (66%) with topical isotretinoin 0.1% (0.5 g; applied once daily for 36 weeks)<br>55/358 (15%) with vehicle cream (applied once daily for 36 weeks) | RR 4.31<br>95% CI 3.34 to 5.57 | ●●○ | vehicle cream |
| [22] RCT | 776 people in 17 US centres, aged 20–76 years, with mild to moderate facial photodamage | **Withdrawal because of adverse effects**<br>5/307 (1.6%) with topical isotretinoin 0.05% (applied once daily for 12 weeks), followed by isotretinoin 0.01% (applied for the next 24 weeks)<br>1/306 (0.3%) with vehicle cream (applied for 36 weeks)<br>The RCT reported that severe intolerability reactions, which were unspecified, occurred in "less than 5% of people" taking isotretinoin | Significance not assessed | | |

**Further information on studies**

[22] Five dermatologists assessed pre- and post-treatment photographs. The RCT reported that all dermatologists found that isotretinoin significantly improved fine wrinkles compared with vehicle cream (P <0.05).

**Comment:** The RCTs provide limited evidence on the effectiveness of isotretinoin 0.1% in the treatment of wrinkles, and so more studies are needed to confirm these findings.

## OPTION ALPHA AND BETA HYDROXYL ACIDS

- For GRADE evaluation of interventions for Wrinkles, see table, p 41 .
- We don't know whether alpha or beta hydroxyl acids are beneficial.

### Benefits and harms

**Glycolic acid versus vehicle cream:**

We found one systematic review (search date 2002, 2 RCTs, 149 people with mild to moderate photodamage). [14] The systematic review did not perform a meta-analysis.

**Wrinkle improvement**

*Glycolic acid compared with placebo* Glycolic acid 8% may be more effective than placebo at improving fine wrinkles after 12 to 22 weeks (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Improvement in fine wrinkles** | | | | | |
| [14] Systematic review | 75 people<br>Data from 1 RCT | **Improvement in fine wrinkles , 12 weeks**<br>with glycolic acid 5% (applied for 12 weeks)<br>with vehicle cream (applied for 12 weeks)<br>Initially, creams were applied once every 2 days. If there was no irritation after the first week, creams were applied once daily, and then, after 2 weeks, twice daily | WMD –0.42<br>95% CI –1.68 to +0.84 | ⟷ | Not significant |
| [23] RCT **3-armed trial** | 74 women<br>In review [14]<br>The remaining arm evaluated lactic acid 8% applied twice daily | **Physician-assessed improvement of fine facial wrinkling (measured on a 10-point scale: 0 = none and 9 = severe) , 22 weeks**<br>22% with glycolic acid 8% (applied twice daily)<br>15% with vehicle cream (applied twice daily) | P <0.05 | ○○○ | glycolic acid 8% |
| [23] RCT **3-armed trial** | 74 women<br>In review [14]<br>The remaining arm evaluated lactic acid 8% applied twice daily | **Mean grade change of physician-assessed fine facial wrinkling (measured on a 10-point scale: 0 = none and 9 = severe) , 22 weeks**<br>–1.14 with glycolic acid 8% (applied twice daily)<br>–0.86 with vehicle cream (applied twice daily) | P <0.05 | ○○○ | glycolic acid 8% |

### Quality of life

No data from the following reference on this outcome. [14]

### Adverse effects

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Adverse effects** | | | | | |
| [14]<br>Systematic review | 75 people<br>Data from 1 RCT | **Adverse effects**<br>with glycolic acid 5% (applied twice daily)<br>with vehicle cream (applied twice daily)<br>No major adverse effects or complications were associated with glycolic acid 5% | | | |
| [23]<br>RCT<br>**3-armed trial** | 74 women<br>In review [14] | **Adverse effects**<br>with glycolic acid 8% (applied twice daily)<br>with lactic acid 8% (applied twice daily)<br>with vehicle cream (applied twice daily)<br>30% of people had some degree of erythema at one or more treatment sites | | | |

**Lactic acid versus vehicle cream:**

We found one systematic review (search date 2002, 2 RCTs, 149 people with mild to moderate photodamage). [14] The review identified one RCT assessing lactic acid. [23]

### Wrinkle improvement

*Lactic acid compared with placebo* Lactic acid 8% may be more effective than placebo at improving fine wrinkles after 22 weeks (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Improvement in fine wrinkles** | | | | | |
| [23]<br>RCT<br>**3-armed trial** | 74 women<br>In review [14]<br>The remaining arm evaluated glycolic acid 8% applied twice daily | **Physician-assessed improvement of fine facial wrinkling (measured on a 10-point scale: 0 = none and 9 = severe) , 22 weeks**<br>22% with lactic acid 8% (applied twice daily)<br>15% with vehicle cream (applied twice daily) | P <0.05 | ○○○ | lactic acid 8% |
| [23]<br>RCT | 74 women<br>In review [14]<br>The remaining arm evaluated glycolic | **Mean grade change of physician-assessed fine facial wrinkling (measured on a 10-point scale: 0 = none and 9 = severe) , 22 weeks** | P <0.05 | ○○○ | lactic acid 8% |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **3-armed trial** | acid 8% applied twice daily | –1.04 with lactic acid 8% (applied twice daily)<br>–0.86 with vehicle cream (applied twice daily) | | | |

### Quality of life

No data from the following reference on this outcome. [14]

### Adverse effects

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Adverse effects** | | | | | |
| [23]<br>RCT<br>**3-armed trial** | 74 women<br>In review [14] | **Adverse effects**<br>with glycolic acid 8% (applied twice daily)<br>with lactic acid 8% (applied twice daily)<br>with vehicle cream (applied twice daily)<br>30% of people had some degree of erythema at one or more treatment sites | | | |

**Comment:** The effectiveness of glycolic acid and lactic acid in the treatment of wrinkles is based on data from RCTs that reported the mean change in grade as an outcome. However, whether the mean grade change results in a clinically important improvement is not clear.

## OPTION CARBON DIOXIDE LASER

- For GRADE evaluation of interventions for Wrinkles, see table, p 41 .
- We don't know whether carbon dioxide laser is better than no active treatment in people with wrinkles, as we found no direct evidence.
- We don't know whether carbon dioxide laser is more effective than dermabrasion, chemical peel, erbium:YAG laser or carbon dioxide laser plus variable pulse erbium:YAG laser at improving wrinkles, as studies have given inconclusive results.
- Adverse effects are common with carbon dioxide laser, especially erythema.

### Benefits and harms

**Carbon dioxide laser versus placebo/no treatment:**

We found no systematic reviews or RCTs.

### Carbon dioxide laser versus dermabrasion:

We found one systematic review (search date 2002, [14] 3 RCTs, 55 women with wrinkles) comparing carbon dioxide laser versus dermabrasion.

#### Wrinkle improvement

*Carbon dioxide laser compared with dermabrasion* We don't know how carbon dioxide laser treatment and dermabrasion compare at improving wrinkles (low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Improvement of wrinkles** | | | | | |
| [14] Systematic review | 55 women with wrinkles<br>3 RCTs in this analysis | **Wrinkle score (on a 0–5 scale)**<br>with carbon dioxide laser<br>with dermabrasion<br>RCT reported that carbon dioxide laser produced a better wrinkle score than dermabrasion, but the difference was small | WMD –0.10<br>95% CI –0.35 to +0.16 | ⟷ | Not significant |

#### Quality of life

No data from the following reference on this outcome. [14]

#### Adverse effects

*Compared with dermabrasion* Carbon dioxide laser may worsen postoperative erythema and drainage (low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Adverse effects** | | | | | |
| [14] Systematic review | 55 women with wrinkles<br>3 RCTs in this analysis | **Erythema , 1 month**<br>with carbon dioxide laser<br>with dermabrasion<br>See further information on studies for enhanced reporting from one RCT identified by the review<br>See further information on studies for information on withdrawal rates | WMD 0.31<br>95% CI 0.15 to 0.47 | ○○○ | dermabrasion |
| [24] RCT | 20 women with wrinkles<br>In review [14] | **Hypertrophic scar**<br>with carbon dioxide laser<br>with dermabrasion<br>One woman developed a hypertrophic scar on the side treated with dermabrasion | | | |
| [24] RCT | 20 women with wrinkles<br>In review [14] | **Herpetic lesions**<br>with carbon dioxide laser<br>with dermabrasion<br>Three people developed herpetic lesions several days after treatment, despite valaciclovir prophylaxis | | | |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| [24] RCT | 20 women with wrinkles In review [14] | **Proportion of people reporting worse "post-treatment drainage" with each intervention** 10/20 (50%) with carbon dioxide laser 2/20 (10%) with dermabrasion | P = 0.002 | ○○○ | dermabrasion |

### Carbon dioxide laser versus chemical peel:

We found one systematic review (search date 2002, [14] 1 RCT, 20 women) and one additional RCT. [25]

#### Wrinkle improvement

*Carbon dioxide laser compared with chemical peel* We don't know how carbon dioxide laser treatment and chemical peel compare at improving wrinkles (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Improvement in wrinkles** | | | | | |
| [26] RCT | 20 women, aged 51–71 years, with Fitzpatrick skin type I–III and with wrinkles on upper lip In review [14] | **Average change in upper lip wrinkle score (6-point scale: 0 = none to 5 = severe) , baseline to 6 months** from 4.30 to 1.11 with carbon dioxide laser from 4.20 to 0.47 with baker's phenol chemical peel The change from baseline was statistically significant for both carbon dioxide laser and chemical peel (P <0.001) | P <0.03 | ○○○ | baker's phenol chemical peel |
| [25] RCT | 24 men and women, aged 43–73 years, with Fitzpatrick skin types I–III Within participant comparison (opposite sides of the face) | **Severity of periorbital wrinkles (6-point scale: 0 = none to 5 = severe) , baseline to 6 months** from 4.00 to 1.75 with carbon dioxide laser from 4.13 to 3.29 with trichloroacetic acid chemical peel Investigators and participants were not blinded to treatment allocation, but an independent blinded investigator assessed outcomes | P <0.001 | ○○○ | carbon dioxide laser |

#### Quality of life

No data from the following reference on this outcome. [14] [25]

#### Adverse effects

*Carbon dioxide laser compared with chemical peel* We don't know whether carbon dioxide laser is associated with an increased risk of adverse effects, including erythema, scarring, herpes simplex infection, contact dermatitis, hypopigmentation, or whitehead formation (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Adverse effects** | | | | | |
| [26]<br>RCT | 20 women, aged 51–71 years, with Fitzpatrick skin type I–III and with wrinkles on upper lip<br>In review [14] | **Erythema**<br>with carbon dioxide laser<br>with baker's phenol chemical peel<br>55% of people had erythema coagulum on the upper lip or both lips; in 10% of people it was more severe on the laser treated side, and in 35% of people this was more severe on the chemical peel side | | | |
| [26]<br>RCT | 20 women, aged 51–71 years, with Fitzpatrick skin type I–III and with wrinkles on upper lip<br>In review [14] | **Hypertrophic scar**<br>with carbon dioxide laser<br>with baker's phenol chemical peel<br>One person developed an 8 mm hypertrophic scar on the phenol-treated side | | | |
| [26]<br>RCT | 20 women, aged 51–71 years, with Fitzpatrick skin type I–III and with wrinkles on upper lip<br>In review [14] | **Herpes simplex infection**<br>with carbon dioxide laser<br>with baker's phenol chemical peel<br>Herpes simplex infection was reported in three people, which responded to valaciclovir (treatment side not reported) | | | |
| [25]<br>RCT | 24 men and women, aged 43–73 years, with Fitzpatrick skin types I–III<br>Within-participant comparison (opposite sides of the face) | **Mean length of erythema duration**<br>4.5 months with carbon dioxide laser<br>2.5 months with trichloroacetic acid chemical peel | | | |
| [25]<br>RCT | 24 men and women, aged 43–73 years, with Fitzpatrick skin types I–III<br>Within-participant comparison (opposite sides of the face) | **Scarring**<br>13/24 (52%) with carbon dioxide laser<br>3/24 (13%) with trichloroacetic acid chemical peel<br>All scars improved or resolved after treatment with topical silicone paste or intralesional corticosteroids | | | |
| [25]<br>RCT | 24 men and women, aged 43–73 years, with Fitzpatrick skin types I–III<br>Within-participant comparison (opposite sides of the face) | **Contact dermatitis to bacitracin–polymyxin B ointment**<br>with carbon dioxide laser<br>with trichloroacetic acid chemical peel<br>Occurred in four people; symptoms resolved after switching topical treatment to petrolatum and a low-potency topical corticosteroid | | | |
| [25]<br>RCT | 24 men and women, aged 43–73 years, with Fitzpatrick skin types I–III | **Hypopigmentation**<br>with carbon dioxide laser<br>with trichloroacetic acid chemical peel | | | |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| | Within-participant comparison (opposite sides of the face) | Hypopigmentation developed in 6/24 (25%) people in the carbon dioxide laser-treated arm, but resolved or improved by the end of the study; no further data reported | | | |
| [25]<br>RCT | 24 men and women, aged 43–73 years, with Fitzpatrick skin types I–III<br>Within-participant comparison (opposite sides of the face) | **Whitehead formation**<br>with carbon dioxide laser<br>with trichloroacetic acid chemical peel<br>Whitehead formation was relatively common during the prolonged healing phase, but resolved or improved with tretinoin or manual extraction (no data reported) | | | |

No data from the following reference on this outcome. [14]

### Carbon dioxide laser versus erbium:YAG laser:

We found one systematic review (3 RCTs, 55 people). [14] The results of these studies were not combined because of the variability in outcomes.

#### Wrinkle improvement

*Carbon dioxide laser compared with erbium:YAG laser* Carbon dioxide laser may be more effective than erbium:YAG laser (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Improvement in wrinkles** | | | | | |
| [27]<br>RCT | 21 women, aged 39–74 years, with upper lip wrinkles, Fitzpatrick skin types I–IV<br>In review [14]<br>Within-participant comparison (opposite sides of the upper lip) | **Overall wrinkle improvement (not defined) , 2 months**<br>63% with carbon dioxide laser<br>54% with variable pulse erbium:YAG laser<br>Investigators and participants were not blinded to treatment allocation, but a blinded panel of plastic surgeons and trained research assistants assessed outcomes<br>Photographs and digital images of participants were recorded preoperatively and at intervals up to 2 months after treatment | Significance not assessed<br>Results should be interpreted with caution because the participants and investigators were not blinded to treatment allocation | | |
| [28]<br>RCT | 12 women and 1 man, aged 30–80 years, with perioral or periorbital wrinkles, Fitzpatrick skin types I–III<br>In review [14]<br>Within-participant comparison (opposite sides of the face) | **Average improvement in wrinkle score (assessed from photographs; 9-point scale: 0 = absent to 8 = severe)**<br>1–2 points with pulsed carbon dioxide laser (one pass)<br>1–2 points with erbium:YAG laser (four passes)<br>Lasers applied to periorbital or perioral sites, or both<br>Investigators and participants were not blinded to treatment al- | Reported as not significant<br>P value not reported<br>The RCT may have been too small to exclude a clinically important difference<br>Results should be interpreted with caution because the participants and investigators were not blinded to treatment allocation | ⟷ | Not significant |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| | | location, but a blinded panel of physicians familiar with laser resurfacing assessed outcomes | | | |
| [29]<br>RCT | 19 women and 2 men, aged 18–90 years, with perioral or periorbital wrinkles, Fitzpatrick skin types I–III<br>In review [14]<br>Within-participant comparison (opposite sides of the face) | **Wrinkle improvement (measured by aggregate of investigators', participants', and panel's assessments [photographs]) , 6 months**<br>with carbon dioxide laser<br>with variable pulse erbium:YAG laser<br>Absolute results not reported<br>Investigators and participants were not blinded to treatment allocation, but a blinded panel of dermatologists also assessed outcomes | P <0.03<br>Results should be interpreted with caution because the participants and investigators were not blinded to treatment allocation | ○○○ | carbon dioxide laser |

## Quality of life

No data from the following reference on this outcome. [27] [28] [29]

## Adverse effects

*Carbon dioxide laser compared with erbium:YAG laser* Carbon dioxide laser may be associated with a increased risk of hyperpigmentation, hypopigmentation, and prolonged erythema (low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Adverse effects** | | | | | |
| [27]<br>RCT | 21 women, aged 39–74 years, with upper lip wrinkles, Fitzpatrick skin types I–IV<br>In review [14]<br>Within-participant comparison (opposite sides of the upper lip) | **Postoperative erythema**<br>with carbon dioxide laser<br>with variable pulse erbium:YAG laser<br>Postoperative erythema occurred with both treatments<br>Investigators and participants were not blinded to treatment allocation, but a blinded panel of plastic surgeons and trained research assistants assessed outcomes<br>Photographs and digital images of participants were recorded preoperatively and at intervals up to 2 months after treatment | Reported as not significant<br>P value not reported | ⟷ | Not significant |
| [27]<br>RCT | 21 women, aged 39–74 years, with upper lip wrinkles, Fitzpatrick skin types I–IV<br>In review [14]<br>Within-participant comparison (opposite sides of the upper lip) | **Hyperpigmentation**<br>with carbon dioxide laser<br>with variable pulse erbium:YAG laser<br>One person had mild hyper-pigmentation at about 4 weeks with erbium:YAG laser, which cleared by 3 months<br>Investigators and participants were not blinded to treatment allocation, but a blinded panel of | | | |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| | | plastic surgeons and trained research assistants assessed outcomes<br>Photographs and digital images of participants were recorded preoperatively and at intervals up to 2 months after treatment | | | |
| [28]<br>RCT | 12 women and 1 man, aged 30–80 years, with perioral or periorbital wrinkles, Fitzpatrick skin types I–III<br>In review [14]<br>Within-participant comparison (opposite sides of the face) | **Postoperative erythema , 2 weeks**<br>with pulsed carbon dioxide laser (one pass)<br>with erbium:YAG laser (four passes)<br>Lasers applied to periorbital or perioral sites, or both. Investigators and participants were not blinded to treatment allocation, but a blinded panel of physicians familiar with laser resurfacing assessed outcomes | P <0.04 | ○○○ | carbon dioxide laser |
| [28]<br>RCT | 12 women and 1 man, aged 30–80 years, with perioral or periorbital wrinkles, Fitzpatrick skin types I–III<br>In review [14]<br>Within-participant comparison (opposite sides of the face) | **Postoperative erythema , 2 and 6 months**<br>with pulsed carbon dioxide laser (one pass)<br>with erbium:YAG laser (four passes)<br>Rates of postoperative erythema were similar between the two groups at 2 and 6 months<br>Lasers applied to periorbital or perioral sites, or both. Investigators and participants were not blinded to treatment allocation, but a blinded panel of physicians familiar with laser resurfacing assessed outcomes | | | |
| [28]<br>RCT | 12 women and 1 man, aged 30–80 years, with perioral or periorbital wrinkles, Fitzpatrick skin types I–III<br>In review [14]<br>Within-participant comparison (opposite sides of the face) | **Hyperpigmentation**<br>with pulsed carbon dioxide laser (one pass)<br>with erbium:YAG laser (four passes)<br>Lasers applied to periorbital or perioral sites, or both<br>Investigators and participants were not blinded to treatment allocation, but a blinded panel of physicians familiar with laser resurfacing assessed outcomes | Reported as not significant<br>P value not reported | ⟷ | Not significant |
| [29]<br>RCT | 19 women and 2 men, aged 18–90 years, with perioral or periorbital wrinkles, Fitzpatrick skin types I–III<br>In review [14]<br>Within-participant comparison (opposite sides of the face) | **Erythema , 2 weeks**<br>95% with carbon dioxide laser<br>67% with variable pulse erbium:YAG laser<br>Investigators and participants were not blinded to treatment allocation, but a blinded panel of dermatologists also assessed outcomes | | | |
| [29] | 19 women and 2 men, aged 18–90 | **Erythema , 2 months** | | | |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| RCT | years, with perioral or periorbital wrinkles, Fitzpatrick skin types I–III<br>In review [14]<br>Within-participant comparison (opposite sides of the face) | 62% with carbon dioxide laser<br>24% with variable pulse erbium:YAG laser<br>Investigators and participants were not blinded to treatment allocation, but a blinded panel of dermatologists also assessed outcomes | | | |
| [29]<br>RCT | 19 women and 2 men, aged 18–90 years, with perioral or periorbital wrinkles, Fitzpatrick skin types I–III<br>In review [14]<br>Within-participant comparison (opposite sides of the face) | **Mild erythema , 6 months**<br>10% with carbon dioxide laser<br>0% with variable pulse erbium:YAG laser<br>Investigators and participants were not blinded to treatment allocation, but a blinded panel of dermatologists also assessed outcomes | | | |
| [29]<br>RCT | 19 women and 2 men, aged 18–90 years, with perioral or periorbital wrinkles, Fitzpatrick skin types I–III<br>In review [14]<br>Within-participant comparison (opposite sides of the face) | **Hypopigmentation**<br>43% with carbon dioxide laser<br>5% with variable pulse erbium:YAG laser<br>Some hypo-pigmentation was still visible at 6 months<br>Investigators and participants were not blinded to treatment allocation, but a blinded panel of dermatologists also assessed outcomes | P <0.05 | ○○○ | variable pulse erbium:YAG laser |
| [29]<br>RCT | 19 women and 2 men, aged 18–90 years, with perioral or periorbital wrinkles, Fitzpatrick skin types I–III<br>In review [14]<br>Within-participant comparison (opposite sides of the face) | **Hyperpigmentation**<br>29% with carbon dioxide laser<br>24% with variable pulse erbium:YAG laser<br>Hyperpigmentation resolved spontaneously in all cases within 6 months<br>Investigators and participants were not blinded to treatment allocation, but a blinded panel of dermatologists also assessed outcomes | | | |

No data from the following reference on this outcome. [14]

### Carbon dioxide laser versus carbon dioxide laser plus variable pulse erbium:YAG laser:

We found one systematic review (1 double blind RCT, 20 women). [14]

#### Wrinkle improvement

*Carbon dioxide laser compared with carbon dioxide laser plus variable pulse erbium:YAG laser* We don't know how carbon dioxide laser and carbon dioxide laser plus variable pulse erbium:YAG laser compare at improving wrinkles (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Improvement in wrinkles** | | | | | |
| [14] Systematic review | 20 women, aged 42–72 years, with Fitzpatrick skin types I–III on the upper lip<br>Data from 1 RCT | **Wrinkle improvement , 4 months**<br>67% with carbon dioxide laser alone<br>68% with carbon dioxide laser plus variable pulse erbium:YAG laser | Reported as not significant<br>P value not reported | ⟷ | Not significant |

### Quality of life

No data from the following reference on this outcome. [14]

### Adverse effects

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Adverse effects** | | | | | |
| [14] Systematic review | 20 women, aged 42–72 years, with Fitzpatrick skin types I–III on the upper lip<br>Data from 1 RCT | **Erythema**<br>with carbon dioxide laser alone<br>with carbon dioxide laser plus variable pulse erbium:YAG laser | Reported as not significant<br>P value not reported | ⟷ | Not significant |
| [14] Systematic review | 20 women, aged 42–72 years, with Fitzpatrick skin types I–III on the upper lip<br>Data from 1 RCT | **Pain**<br>with carbon dioxide laser alone<br>with carbon dioxide laser plus variable pulse erbium:YAG laser | Reported as not significant<br>P value not reported | ⟷ | Not significant |

**Further information on studies**

[14] **Carbon dioxide laser versus dermabrasion:** Two of the RCTs included in the review reported withdrawal rates of 1/20 (5%) [24] and 1/15 (7%). [30] The third RCT gave no information on withdrawal rates.

[24] [14] **Carbon dioxide laser versus dermabrasion:** In the RCT [24] identified by the review, [14] 85% of women (20 women in RCT) had erythema on the upper lip (similar for both groups) 1 month after treatment. In 10% of people, erythema was reported to be worse on the laser-treated side, and in 5%, on the dermabrasion-treated side. The average duration of erythema was 2.5 months for both treatments. Pain, oedema, eczema, and whiteheads resolved either spontaneously or with minimal treatment.

**Comment:** The effects of chemical peels and $CO_2$ lasers are likely to be dependent on the technique of the dermatological surgeon; therefore, results may not generalise to different populations. [14] The available evidence is too weak to define the effects of $CO_2$ laser on wrinkles.

## OPTION CHEMICAL PEEL

- For GRADE evaluation of interventions for Wrinkles, see table, p 41 .
- We don't know whether chemical peels are beneficial.

### Benefits and harms

**Chemical peel versus placebo/no treatment:**

We found no systematic review or RCTs.

**Chemical peel versus carbon dioxide laser:**

See option on carbon dioxide laser, p 23 .

**Comment:** **Chemical peel versus carbon dioxide laser:**
See comment on carbon dioxide laser, p 23 .

## OPTION DERMABRASION

- For GRADE evaluation of interventions for Wrinkles, see table, p 41 .
- We found no direct information about whether dermabrasion is better than no active treatment.
- We don't know whether dermabrasion is more effective at improving wrinkles compared with carbon dioxide laser treatment, as studies have given inconclusive results, but adverse effects are common with both treatments, especially erythema.

### Benefits and harms

**Dermabrasion versus placebo/control:**

We found no systematic reviews or RCTs.

**Dermabrasion versus carbon dioxide laser:**

See option on carbon dioxide laser, p 23 .

**Comment:** None.

## OPTION FACELIFT

- For GRADE evaluation of interventions for Wrinkles, see table, p 41 .
- We don't know whether facelifts improve wrinkles, as we found no direct information about their effects on wrinkles.

### Benefits and harms

**Facelift:**

We found no systematic review and no RCTs.

**Comment:** **Clinical guide:**
The effectiveness and safety of facelift surgery is likely to depend on the technique of the surgeon.

## OPTION ORAL NATURAL CARTILAGE POLYSACCHARIDES

- For GRADE evaluation of interventions for Wrinkles, see table, p 41 .
- We don't know whether oral natural cartilage polysaccharides are beneficial.

## Benefits and harms

### Oral natural cartilage polysaccharides versus placebo:

We found one systematic review (search date 2002, 1 RCT) [14] and one additional RCT. [31]

#### Wrinkle improvement

*Oral natural cartilage polysaccharides compared with placebo* We don't know whether an oral preparation of cartilage polysaccharide is more effective at 3 months (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Improvement in fine wrinkles** | | | | | |
| [32]<br>RCT | 30 women, aged 40–60 years, with moderate to severe wrinkles<br>In review [14] | **Proportion of women with improved facial fine wrinkles , 90 days**<br>10/15 (67%) with oral cartilage polysaccharide preparation (Vivida® 500 mg/day)<br>0/15 (0%) with placebo<br>Wrinkles were graded as severe, moderate or absent, without a grading of "mild". It could be expected that wrinkles would have reduced from moderate/severe to mild rather than to absent | RR 21.0, 95% CI 1.34 to 328.86<br>The RCT was small, and the possibility of publication bias cannot be excluded | ●●● | oral natural cartilage polysaccharide |
| [31]<br>RCT | 144 people, aged 35–50 years, with Fitzpatrick skin type II or III and mild to moderate photoaging | **Improvement in face or eye wrinkles (physician assessed and participant assessed using a 10 cm visual analogue scale, dermatologist assessed using photographs) , 3 months**<br>with cartilage polysaccharide preparation (Imedeen® 400 or 200 mg/day for 3 months)<br>with placebo (for 3 months) | Reported as not significant<br>P value not reported | ⟷ | Not significant |

#### Quality of life

No data from the following reference on this outcome. [14] [31]

#### Adverse effects

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Adverse effects** | | | | | |
| [31]<br>RCT | 144 people, aged 35–50 years, with Fitzpatrick skin type II or III and mild to moderate photoaging | **Adverse effects**<br>23/96 [24%] with cartilage polysaccharide preparation (Imedeen® 400 or 200 mg/day for 3 months)<br>10/48 [21%] with placebo (for 3 months)<br>Acne and seborrhoea were the most common skin related events (24/38 [63%]), and oedema and weight increase were the most frequently reported non-skin related events (18/47 [38%]); proportions attributable to active treatment or placebo were not reported | P >0.05 | ⟷ | Not significant |

No data from the following reference on this outcome. [14]

### Oral natural cartilage polysaccharides versus each other:

We found one systematic review (1 RCT, 30 women) comparing two commercial preparations. [14]

#### Wrinkle improvement

*Different oral natural cartilage polysaccharides compared with each other* The Vivida® brand may be more effective than the Imedeen® brand at improving wrinkles (low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Improvement in fine wrinkles** | | | | | |
| [14]<br>Systematic review | 30 women, aged 40–60 years, with moderate to severe wrinkles<br>Data from 1 RCT | **Improvement in fine wrinkles , 90 days**<br>10/15 [66%] with Vivida® 500 mg daily for 90 days<br>3/15 [20%] with Imedeen® 380 mg daily for 90 days | RR 3.33<br>95% CI 1.14 to 9.75 | ●●○ | Vivida® 500 mg |

#### Quality of life

No data from the following reference on this outcome. [14]

#### Adverse effects

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Adverse effects** | | | | | |
| [14]<br>Systematic review | 30 women, aged 40–60 years, with moderate to severe wrinkles | **Adverse effects**<br>with Vivida® 500 mg daily for 90 days | | | |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| | Data from 1 RCT | with Imedeen® 380 mg daily for 90 days<br>No adverse effects were reported for Imedeen®, but 5 women treated with Vivida® developed transient acne-like lesions during the first month of treatment | | | |

**Further information on studies**

**Comment:** The available evidence is inadequate to assess accurately the effects of oral cartilage preparations.

## OPTION RETINYL ESTERS

- For GRADE evaluation of interventions for Wrinkles, see table, p 41 .
- We don't know whether retinyl esters are beneficial.

### Benefits and harms

**Retinyl esters:**

We found no systematic reviews or RCTs.

**Further information on studies**

**Comment:** None.

## OPTION TOPICAL NATURAL CARTILAGE POLYSACCHARIDES

- For GRADE evaluation of interventions for Wrinkles, see table, p 41 .
- We don't know whether topical natural cartilage polysaccharides are beneficial.

### Benefits and harms

**Topical natural cartilage polysaccharides versus placebo:**

We found one systematic review (search date 2002, 1 RCT). [14]

**Wrinkle improvement**

*Topical natural cartilage polysaccharides compared with placebo* A topical preparation of cartilage polysaccharide may be more effective than placebo at reducing fine and coarse wrinkles at 120 days (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Improvement in fine wrinkles** | | | | | |
| [33]<br>RCT | 30 women, aged 40–60 years, with moderate to severe facial wrinkles<br>In review [14]<br>Within-participant comparison (opposite sides of the face) | **Proportion of women with no shallow wrinkles (less than 1 mm) , 120 days**<br>30/30 (100%) with topical cartilage polysaccharide 1% (twice daily for 120 days)<br>0/30 (0%) with placebo (twice daily for 120 days) | P <0.001<br>The clinical importance of this result is unclear; the RCT is limited by its small sample size and by potential difficulties with concealment of allocation<br>Application of creams to each side of the face may result in contamination | ○○○ | topical cartilage polysaccharide |
| [33]<br>RCT | 30 women, aged 40–60 years, with moderate to severe facial wrinkles<br>In review [14]<br>Within-participant comparison (opposite sides of the face) | **Proportion of women with no moderate wrinkles (1 mm) , 120 days**<br>27/30 (90%) with topical cartilage polysaccharide 1% (twice daily for 120 days)<br>0/30 (0%) with placebo (twice daily for 120 days) | P <0.001<br>The clinical importance of this result is unclear; the RCT is limited by its small sample size and by potential difficulties with concealment of allocation<br>Application of creams to each side of the face may result in contamination | ○○○ | topical cartilage polysaccharide |
| **Improvement in coarse wrinkles** | | | | | |
| [33]<br>RCT | 30 women, aged 40–60 years, with moderate to severe facial wrinkles<br>In review [14]<br>Within-participant comparison (opposite sides of the face) | **Proportion of women with no deep wrinkles (greater than 1 mm) , 120 days**<br>5/30 (17%) with topical cartilage polysaccharide 1% (twice daily for 120 days)<br>2/30 (7%) with placebo (twice daily for 120 days) | P <0.001<br>The clinical importance of this result is unclear; the RCT is limited by its small sample size and by potential difficulties with concealment of allocation<br>Application of creams to each side of the face may result in contamination | ○○○ | topical cartilage polysaccharide |

### Quality of life

No data from the following reference on this outcome. [33]

### Adverse effects

No data from the following reference on this outcome. [33]

**Comment:** None.

## OPTION VARIABLE PULSE ERBIUM:YAG LASER

- For GRADE evaluation of interventions for Wrinkles, see table, p 41 .
- We found no direct information from RCTs about whether erbium:YAG laser is better than no active treatment.
- We don't know whether erbium:YAG laser is more effective than carbon dioxide laser at improving wrinkles, as studies have given inconclusive results.

## Benefits and harms

### Variable pulse erbium:YAG laser versus placebo/no treatment:

We found no systematic review or RCTs.

### Variable pulse erbium:YAG laser versus carbon dioxide laser:

See option on carbon dioxide laser, p 23 .

**Comment:** **Variable pulse erbium:YAG laser versus carbon dioxide laser:**
See comment on carbon dioxide laser, p 23 .

## OPTION VITAMIN C OR E (TOPICAL)

- For GRADE evaluation of interventions for Wrinkles, see table, p 41 .
- We don't know whether topical vitamin C improves the appearance of wrinkles, as studies have been small.
- We found no direct information about whether topical vitamin E is better than no active treatment.
- These vitamins may cause stinging and erythema.

## Benefits and harms

### Vitamin C versus placebo:

We found one systematic review (search date 2002), [14] which included one double blind RCT. [34]

**Wrinkle improvement**

*Vitamin C compared with placebo* We don't know whether topical vitamin C is more effective than placebo at improving fine and coarse facial wrinkles (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Improvement in fine wrinkles** | | | | | |
| [34]<br>RCT | 28 people, age 36–72 years, with mild to moderate photodamage<br>In review [14]<br>Within participant comparison (opposite sides of the face) | **Physician-assessed improvement in fine wrinkles (using photographs; graded as "much improved", "improved", "no change", or "worse") , 12 weeks**<br>16/19 (84%) with topical ascorbic acid (0.5 mL) in a vehicle cream (applied once daily for 12 weeks)<br>3/19 (16%) with vehicle cream alone (applied once daily for 12 weeks)<br>Only 19/28 (68%) completed the trial; analysis not by intention to treat | P = 0.002<br>The RCT is limited by its small sample size, short duration and high withdrawal rate, which compromises the validity of the results | ○○○ | ascorbic acid |
| **Improvement in coarse wrinkles** | | | | | |
| [34]<br>RCT | 28 people, age 36–72 years, with mild to moderate photodamage<br>In review [14]<br>Within participant comparison (oppo- | **Physician-assessed improvement in fine wrinkles (using photographs; graded as "much improved", "improved", "no change", or "worse") , 12 weeks** | P = 0.01<br>The RCT is limited by its small sample size, short duration and high withdrawal rate, which compromises the validity of the results | ○○○ | ascorbic acid |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| | site sides of the face) | 13/19 (68%) with topical ascorbic acid (0.5 mL) in a vehicle cream (applied once daily for 12 weeks)<br>3/19 (16%) with vehicle cream alone (applied once daily for 12 weeks)<br>Only 19/28 (68%) completed the trial; analysis not by intention to treat | | | |
| **Improvement in wrinkles (global)** | | | | | |
| [34]<br>RCT | 28 people, age 36–72 years, with mild to moderate photodamage<br>In review [14]<br>Within participant comparison (opposite sides of the face) | **Physician-assessed improvement in fine wrinkles (using photographs; graded as "much improved", "improved", "no change", or "worse") , 12 weeks**<br>16/19 (84%) with topical ascorbic acid (0.5 mL) in a vehicle cream (applied once daily for 12 weeks)<br>3/19 (16%) with vehicle cream alone (applied once daily for 12 weeks)<br>Only 19/28 (68%) completed the trial; analysis not by intention to treat | RR 5.33<br>95% CI 1.85 to 15.34<br>The RCT is limited by its small sample size, short duration and high withdrawal rate, which compromises the validity of the results | ●●● | ascorbic acid |

## Quality of life

No data from the following reference on this outcome. [34]

## Adverse effects

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Adverse effects** | | | | | |
| [34]<br>RCT | 28 people, age 36–72 years, with mild to moderate photodamage<br>In review [14]<br>Within participant comparison (opposite sides of the face) | **Adverse effects**<br>with topical ascorbic acid (0.5 mL) in a vehicle cream (applied once daily for 12 weeks)<br>with vehicle cream alone (applied once daily for 12 weeks)<br>Stinging occurred in 11 (55%) people, erythema in five (24%) people, and dry skin in one (5%) person (data for each group not reported). Symptoms responded to moisturisation and usually resolved within the first 2 months of treatment | | | |

### Vitamin E:

We found no systematic reviews or RCTs.

**Comment:** None.

## GLOSSARY

**Erbium:YAG laser** An yttrium aluminium garnet laser.

**Fitzpatrick skin phototype classification** I = always burns easily, never tans; II = always burns easily, tans minimally; III = burns moderately, tans gradually (light brown); IV = burns minimally, always tans well (brown); V = rarely burns, tans profusely (dark brown); VI = never burns, deeply pigmented (black).

**Mild/moderate/severe photodamage** A spectrum of features including wrinkles, hyperpigmentation, tactile roughness, and telangiectasia. Usually measured on a scale from 0–9 (0 = none, 1–3 = mild, 4–6 = moderate, and 7–9 = severe).

**Low-quality evidence** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low-quality evidence** Any estimate of effect is very uncertain.

## SUBSTANTIVE CHANGES

**Tretinoin** One RCT added comparing tretinoin versus placebo cream in people with sun-damaged skin. [18] It found that tretinoin increased the proportion of people with improved fine wrinkles at 6 months compared with placebo, but also increased skin erythema, peeling, burning, dryness, and itching. Categorisation changed (Trade-off between benefits and harms).

## REFERENCES


1. Green AC. Premature ageing of the skin in a Queensland population. *Clin Exp Dermatol* 1991;155:473–478.
2. Maddin S, Lauharanta J, Agache P, et al. Isotretinoin improves the appearance of photodamaged skin: results of a 36-week, multicenter, double-blind, placebo-controlled trial. *J Int Med Res* 1992;20:381–391.[PubMed]
3. Tsukahara K, Fujimura T, Yoshida Y, et al. Comparison of age-related changes in wrinkling and sagging of the skin in Caucasian females and in Japanese females. *J Cosmet Sci* 2004;55:351–371.[PubMed]
4. Nouveau-Richard S, Yang Z, Mac-Mary S, et al. Skin ageing: a comparison between Chinese and European populations. A pilot study. *J Dermatol Sci* 2005;40:187–193.[PubMed]
5. Nagashima H, Hanada K, Hashimoto I. Correlation of skin phototype with facial wrinkle formation. *Photodermatol Photoimmunol Photomed* 1999;15:2–6.[PubMed]
6. Grady D, Ernster V. Does cigarette smoking make you ugly and old? *Am J Epidemiol* 1992;135:839–842.[PubMed]
7. Affinito P, Palomba S, Sorrentino C, et al. Effects of postmenopausal hypoestrogenism on skin collagen. *Maturitas* 1999;15:239–247.[PubMed]
8. Youn CS, Kwon OS, Won CH, et al. Effect of pregnancy and menopause on facial wrinkling in women. *Acta Derm Venereol* 2003;83:419–424.[PubMed]
9. Gupta MA, Gupta AK. Photodamaged skin and quality of life: reasons for therapy. *J Dermatol Treat* 1996;7:261–264.
10. Alsarraaf R. Outcomes research in facial plastic surgery: a review and new directions. *Aesthetic Plast Surg* 2000;24:192–197.[PubMed]
11. Boyd AS, Naylor M, Cameron GS, et al. The effects of chronic sunscreen use on the histologic changes of dermatoheliosis. *J Am Acad Dermatol* 1995;33:941–946.[PubMed]
12. Green AC. Premature ageing of the skin in a Queensland population. *Med J Aust* 1991;155:473–478.[PubMed]
13. Preventive Services Task Force. Counselling to prevent skin cancer: recommendations and rationale of the U.S. Preventive Services Task Force. *MMWR Recomm Rep* 2003;52:13–17.[PubMed]
14. Samuel M, Brooke RC, Hollis S, et al. Interventions for photodamaged skin. In: The Cochrane Library, Issue 1, 2005. Chichester, UK: John Wiley & Sons, Ltd. Search date 2002.[PubMed]
15. Phillips TJ, Gottlieb AB, Leyden JJ, et al. Efficacy of 0.1% tazarotene cream for the treatment of photodamage. *Arch Dermatol* 2002;138:1486–1493.[PubMed]
16. Kang S, Leyden JJ, Lowe NJ, et al. Tazarotene cream for the treatment of facial photodamage. *Arch Dermatol* 2001;137:1597–1604.[PubMed]
17. Lowe NJ, Gifford M, Tanghetti E, et al. Tazarotene 0.1% cream versus tretinoin 0.05% emollient cream in the treatment of photodamaged facial skin: a multicenter, double-blind, randomized, parallel-group study. *J Cosmet Laser Ther* 2004;6:79–85.[PubMed]
18. Weiss JS, Shavin JS, Nighland M, et al. Tretinoin microsphere gel 0.1% for photodamaged facial skin: a placebo-controlled trial. *Cutis* 2006;78:426–432.[PubMed]
19. Lipson AH, Collins F, Webster WS. Multiple congenital defects associated with maternal use of topical tretinoin. *Lancet* 1993;341:1352–1353.[PubMed]
20. Camera G, Pregliasco P. Ear malformation in baby born to mother using tretinoin cream. *Lancet* 1992;339:687.[PubMed]
21. Jick SS, Terris BZ, Jick H. First trimester topical tretinoin and congenital disorders. *Lancet* 1993;341:1181–1182.[PubMed]
22. Sendagorta E, Lesiewicz J, Armstrong RB. Topical isotretinoin for photodamaged skin. *J Am Acad Dermatol* 1992;27:S15–S18.[PubMed]
23. Stiller MJ, Bartolone J, Stern R, et al. Topical 8% glycolic acid and 8% L-lactic acid creams for the treatment of photodamaged skin. A double-blind vehicle-controlled clinical trial. *Arch Dermatol* 1996;132:631–636.[PubMed]
24. Gin I, Chew J, Rau KA, et al. Treatment of upper lip wrinkles: a comparison of the 950 µsec dwell time carbon dioxide laser to manual tumescent dermabrasion. *Dermatol Surg* 1999;25:468–474.[PubMed]
25. Reed JT, Joseph AK, Bridenstine JB. Treatment of periorbital wrinkles. A comparison of the SilkTouch carbon dioxide laser with a medium-depth chemical peel. *Dermatol Surg* 1997;23:643–648. [PubMed]
26. Chew J, Gin I, Rau KA, et al. Treatment of upper lip wrinkles: a comparison of 950 microsec dwell time carbon dioxide laser with unoccluded baker's phenol chemical peel. *Dermatol Surg* 1999;25:262–266.[PubMed]
27. Newman JB, Lord JL, Ash K, et al. Variable pulse erbium:YAG laser skin resurfacing of perioral rhytides and side-by-side comparison with carbon dioxide laser. *Lasers Surg Med* 2000;26:208–214.[PubMed]
28. Ross EV, Miller C, Meehan K, et al. One-pass CO2 versus multiple-pass Er:YAG laser resurfacing in the treatment of rhytides: a comparison side-by-side study of pulsed CO2 and Er:YAG lasers. *Dermatol Surg* 2001;27:709–715.[PubMed]
29. Khatri KA, Ross V, Grevelink LM, et al. Comparison of erbium:YAG and carbon dioxide lasers in resurfacing of facial rhytides. *Arch Dermatol* 1999;135:391–397.[PubMed]
30. Holmkvist KA, Rogers GS. Treatment of perioral rhytides. *Arch Dermatol* 2000;136:725–731.[PubMed]
31. Kieffer ME, Efsen J. Imedeen® in the treatment of photoaged skin: an efficacy and safety trial over 12 months. *J Eur Acad Dermatol Venereol* 1998;11:129–136.[PubMed]
32. Eskelinen A, Santalahti J. Special natural cartilage polysaccharides for the treatment of sun-damaged skin in females. *J Int Med Res* 1992;20:99–105.[PubMed]
33. Lassus A, Eskelinen A, Santalahti J. The effect of Vivida® cream as compared with placebo cream in the treatment of sun-damaged or age-damaged facial skin. *J Int Med Res* 1992;20:381–391.[PubMed]
34. Traikovich SS. Use of topical ascorbic acid and its effects on photodamaged skin topography. *Arch Otolaryngol Head Neck Surg* 1999;125:1091–1098.[PubMed]

# Wrinkles

**Juan Jorge Manríquez**
Unidad Docente Asociada de Dermatologia
School of Medicine, Pontificia Universidad Catolica de Chile
Santiago
Chile

**Daniela Majerson Gringberg**
Pontificia Universidad Católica de Chile
Santiago
Chile

**Claudia Nicklas Diaz**
MD
Universidad de La Frontera
Temuco
Chile

Competing interests: JM, DMG, and CND declare that they have no competing interests.

## Disclaimer

**GRADE** **Evaluation of interventions for Wrinkles.**

| Important outcomes | | | Adverse effects, Quality of life, Wrinkle improvement | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Studies (Participants) | Outcome | Comparison | Type of evidence | Quality | Consistency | Directness | Effect size | GRADE | Comment |
| *What are the effects of treatments for skin wrinkles?* | | | | | | | | | |
| 2 (912) [15] [16] | Wrinkle improvement | Tazarotene versus vehicle cream | 4 | –1 | –1 | 0 | 0 | Low | Quality point deducted for incomplete reporting of results. Consistency point deducted for inconsistent effect with different doses |
| 2 (291) [14] [17] | Wrinkle improvement | Tazarotene versus tretinoin | 4 | –2 | –1 | 0 | 0 | Very low | Quality points deducted for uncertainty about randomisation and allocation concealment, and inconsistent assessment of results. Consistency point deducted for conflicting results |
| 13 (1480) [14] [18] | Wrinkle improvement | Tretinoin versus placebo | 4 | –3 | 0 | 0 | 0 | Very low | Quality points deducted for uncertainty about randomisation and allocation concealment, inconsistent assessment of results, and short-term follow-up in some RCTs. Consistency point deducted for conflicting results, but added for dose response |
| 2 (1099) [14] [22] | Wrinkle improvement | Isotretinoin versus placebo | 4 | –3 | 0 | 0 | 0 | Very low | Quality points deducted for poor follow-up, no intention-to-treat analysis, and incomplete reporting of results |
| 2 (149) [14] | Wrinkle improvement | Glycolic acid versus vehicle cream | 4 | –2 | 0 | –1 | 0 | Very low | Quality points deducted for sparse data, and incomplete reporting of results. Directness point deducted for uncertainty about clinical significance of the outcome. Consistency point deducted for conflicting results, but added for possible dose response |
| 1 (74) [14] | Wrinkle improvement | Lactic acid versus vehicle cream | 4 | –2 | 0 | –1 | 0 | Very low | Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for uncertainty about clinical significance of the outcome |
| 3 (55) [14] | Wrinkle improvement | Carbon dioxide laser versus dermabrasion | 4 | –2 | 0 | 0 | 0 | Low | Quality points deducted for sparse data and incomplete reporting of results |
| 3 (55) [14] | Adverse effects | Carbon dioxide laser versus dermabrasion | 4 | –2 | 0 | 0 | 0 | Low | Quality points deducted for sparse data and incomplete reporting of results |
| 2 (44) [14] [25] | Wrinkle improvement | Carbon dioxide laser versus chemical peel | 4 | –3 | –1 | 0 | 0 | Very low | Quality points deducted for sparse data, inadequate blinding and incomplete reporting of results. Consistency point deducted for contradictory results |
| 2 (44) [26] [25] | Adverse effects | Carbon dioxide laser versus chemical peel | 4 | –3 | –1 | 0 | 0 | Very low | Quality points deducted for sparse data, inadequate blinding and incomplete reporting of results. Consistency point deducted for contradictory results |
| 3 (55) [27] [28] [29] | Wrinkle improvement | Carbon dioxide laser versus erbium:YAG laser | 4 | –3 | –1 | –1 | 0 | Very low | Quality points deducted for sparse data, incomplete blinding, and incomplete reporting of results. Consistency point deducted for conflicting results. Directness point deducted for different outcomes assessed |
| 3 (55) [27] [28] [29] | Adverse effects | Carbon dioxide laser versus erbium:YAG laser | 4 | –2 | 0 | 0 | 0 | Low | Quality points deducted for sparse data, and incomplete reporting of results |
| 1 (20) [14] | Wrinkle improvement | Carbon dioxide laser versus carbon dioxide laser plus variable pulse erbium:YAG laser | 4 | –3 | 0 | 0 | 0 | Very low | Quality point deducted for sparse data, incomplete blinding, and incomplete reporting of results |

| Important outcomes | | | Adverse effects, Quality of life, Wrinkle improvement | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Studies (Participants)** | **Outcome** | **Comparison** | **Type of evidence** | **Quality** | **Consistency** | **Directness** | **Effect size** | **GRADE** | **Comment** |
| 2 (174) [14] [31] | Wrinkle improvement | Oral natural cartilage polysaccharides versus placebo | 4 | –3 | –1 | 0 | 0 | Very low | Quality points deducted for sparse data, flawed assessment of outcome and incomplete reporting of results. Consistency point deducted for conflicting results |
| 1 (30) [14] | Wrinkle improvement | Oral natural cartilage polysaccharides versus each other | 4 | –2 | 0 | 0 | 0 | Low | Quality points deducted for sparse data and flawed outcome assessment |
| 1 (30) [33] | Wrinkle improvement | Topical natural cartilage polysaccharides versus placebo | 4 | –2 | 0 | –1 | 0 | Very low | Quality points deducted for sparse data and flawed allocation concealment. Directness point deducted for uncertainty about clinical significance of outcome |
| 1 (28) [34] | Wrinkle improvement | Vitamin C versus placebo | 4 | –3 | 0 | 0 | 0 | Very low | Quality points deducted for sparse data, poor follow-up, and no intention-to-treat analysis |

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.